A randomized trial of the Tubulcus multilayer bandaging system in the treatment of extensive venous ulcers

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Background: **Venous ulcers are a major health problem because of their high prevalence and associated high cost of care. Compression therapy is the most widely used treatment for this condition. The vast majority of published articles on compression therapy present the results in the treatment of venous ulcers usually up to 15 to 20 cm^2. However, there are no published data in English medical literature on the efficacy of compression therapy in the treatment of extensive venous ulcers (ulcers >20 cm^2 of more than 6 months' duration) with regard to healing rate, time to healing, and recurrence rate at 12 months after healing.**

Methods: **A total of 138 patients with extensive venous ulceration (ulceration surface, 20-210 cm^2; duration, 7 months to 28 years) were randomized into 2 groups: (1) a treatment group (72 patients who were treated by using a multilayer bandaging system with the Tubulcus (a heelless open-toed elastic compression device knitted in tubular form) and elastic bandages and (2) a control group (66 patients treated with a multilayer bandaging system with elastic bandages only). The patients were treated on an ambulatory basis; the primary end point of the study was complete ulcer healing at 500 days. The secondary end point was to assess the ulcer recurrence rate during continuation of below-knee compression of different degrees of compression. In the treatment group, patients were instructed to continue to wear the Tubulcus (35 mm Hg), and patients in the control group were instructed to wear compression stockings with compression of 20 to 25 mm Hg. The exclusion criteria from the study were heart insufficiency with an ejection fraction <35, an ankle-brachial pressure index less than 0.8, and pregnancy.**

Results: **The cumulative healing rate was 93% in the treatment group and was 51% in the control group ($P < .001$). The median healing time in the treatment group was 133 days (range, 28 to 464 days), and in the control group it was 211 days (range, 61 to 438 days). The recurrence rate at 12 months in the treatment group was 24% (16/67) and was 53% (18/34) in the control group ($P < .05$). After additional compression treatment with the same treatment protocol, all 16 recurrent ulcers in the treatment group healed. In the control group, the healing rate of recurrent ulcers was 89% (16/18).**

Conclusions: **This study suggests that for extensive venous ulceration, multilayer compression therapy with the Tubulcus provides an extremely high healing rate. Compression of more than 30 mm Hg results in decreased ulcer recurrence. However, recurrence cannot be completely avoided. (J Vasc Surg 2007;46:750-5.)**

Venous ulcers are a major health problem because of their high prevalence and associated high cost of care. Compression therapy is the most widely used treatment for this condition, and it has been used in different forms for more than 350 years.[1] The mechanism of action of compression therapy in the treatment of venous leg ulcers is not completely understood. According to numerous studies, it has been suggested that the application of external pressure to the calf muscle increases the interstitial pressure, thus resulting in improved venous return and reduction in venous hypertension.[2-4] The vast majority of published studies on the treatment of venous leg ulcers using compression therapy are related to venous ulcers smaller than 20 cm^2, and the primary end point is complete ulcer healing at 12 or 24 weeks. However, there are no published data in the English medical literature on the efficacy of the compression therapy in the treatment of extensive venous ulcers (ulcers >20 cm^2 of more than 6 months' duration) with regard to healing rate, time to healing, and recurrence rate at 12 months after healing. Several risk factors have been identified to be correlated with the failure of venous leg ulcers to heal with compression therapy: longer ulcer duration, large surface area, fibrinous deposition present on more than 50% of the wound surface, and an ankle-brachial pressure index of less than 0.8.[5] The purpose of this study was to compare the efficacy and safety of two different multilayer bandaging systems in the treatment of extensive venous ulcers.

METHODS

With a power of 80% ($\beta = 20\%$) and a significance level of $\alpha = 5\%$, assuming a healing rate of 80%, with the recruitment period of 1 year (considering the difference

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between the examined groups to be 0.400 times the within-patient standard deviation), 120 patients were needed for the study. Because the patient population included in this study could differ to some extent, and allowing for a dropout rate of 10% to 20%, a sample size of 150 patients was calculated to be required for the study.

Patients aged at least 18 years with leg ulceration of venous etiology were screened for inclusion in the trial. Before randomization, all patients underwent color duplex scan examination and ankle-brachial pressure index measurements. Examinations were performed by using a Siemens Sonoline Sienna (Erlangen, Germany) ultrasonography device with a 7-MHz probe. Venous compressibility and flow characteristics were the key elements to exclude thrombosis. The direction of flow was assessed in a 20° to 30° reverse Trendelenburg position during the Valsalva maneuver. A cuff inflation-deflation method with rapid cuff deflation in the standing position was performed to induce reflux. The presence of reflux was determined by retrograde flow of longer than 0.5 seconds.

Patients with arterial disease (ankle-brachial pressure index <0.8) and causes of ulceration other than venous disease were excluded from the study. The study also excluded patients with heart insufficiency (ejection fraction <35), pregnancy, cancer disease, and diabetes. Only patients with extensive venous ulcers (surface >20 cm^2 with duration longer than 6 months) were included in the study. Wound size was determined by measurement (maximal length and width) and by a computerized process that consisted of mapping the two-dimensional digital image onto a polygonal mesh.

One hundred seventy-eight patients were considered for the study, and 150 were randomized. Randomization was computer generated, and patients were randomized into two groups. The first group (treatment group) consisted of 75 patients treated with a multilayer bandaging system consisting of a tubular compression device (Tubulcus; Laboratoires Innothera, Arcueil, France) and a medium-stretch compression bandage (100% stretch), 15 cm wide and 5 m long (Niva, Novi Sad, Serbia). The second group (control group) consisted of 75 patients treated with two elastic medium-stretch compression bandages (15 cm $\times$ 5 m, 100% stretch; Niva). Wound swabbing was performed to identify the microbiologic status of the ulcer. If the ulcer did not heal by 250 days, a biopsy was performed.

The study was approved by the relevant authorities, and written consent was obtained from all patients included in the study. All patients in both groups were treated by the same treatment team.

After ulcers have healed, two patients in the treatment group didn't show ulcers during the follow-up period, and one patient had a stroke. In the control group, one patient died in a car accident, and eight patients withdrew their written consent for inclusion into the study, demanding to change treatment groups. A total of 138 patients (72 women and 66 men; mean age, 56 years) with extensive venous ulceration (ulceration surface, 20-210 cm^2; duration, 7 months to 28 years) completed the study (72 patients in the treatment group and 66 patients in the control group). The patients were treated on ambulatory basis, and the primary end point of the study was complete ulcer healing at 500 days. The secondary end point was to assess the ulcer recurrence rate during the continuation of below-knee compression of different degrees of compression. In the treatment group, patients were instructed to continue to wear the Tubulcus (35 mm Hg), and patients in the control group were instructed to wear compression stockings with compression of 20 to 25 mm Hg (Rudo, Nis, Serbia). Patients were reviewed every 2 months during the 1-year follow-up period and were advised to continue wearing stockings long-term, although compliance was not formally assessed. Stockings were replaced every 6 months. All patients were advised to return to the clinic if ulceration recurred.

Treatment regimen. The standard regimen was to debride the wound. This was normally simple mechanical debridement with sterile gauze to remove slough and other dead tissue. According to the extent of wound exudation, dressings were changed every 1 to 7 days. Extensive wound exudation was treated with crystal acidum boricum (after debridement, acidum boricum was applied over the wound in a thin layer), and in patients with no exudation, dry dressings were performed. No antibiotics were used, and patients in both groups received only aspirin (100 mg). After wound debridement and dressing, bandaging systems were applied. The bandaging systems were applied as follows.

The first and second layers in both groups were the same: cotton gauze without tension (50% overlap) and cotton crepe bandage. The third layer in the treatment group consisted of a ready-made knee-length tubular compression device (Tubulcus) that exerts graduated pressure, with the highest compression (35-40 mm Hg) at the ankle, diminishing up the calf. Device size was determined for each patient according to the circumferences of the leg measured at the ankle and the largest part of the calf (five sizes—S, M, L, XL, and XXL—were available). The circumference of the limb was measured every 4 weeks during the treatment, and according to these measurements a Tubulcus was applied. If the measurements of the limb stayed at the initial size, the Tubulcus was changed after 6 months. The first step to put on the compression device is the placement of the positioner on the lower leg (over the local dressing). Then the device is slipped over the positioner to the desired position. The positioner is then removed by pulling it down by the handle toward the opening in the foot section. As the positioner is gliding on itself and not on the local dressing, there is no danger that the dressing moves down when the device is pulled off.[6]

The third layer in the control group was elastic medium-stretch bandage (100% stretch), 15 cm wide and 5 m long, in a spiral with a 50% overlap, and the fourth layer in both groups was the same: medium-stretch elastic bandage (100% stretch), 15 cm wide and 5 m long, in a spiral with a 50% overlap. The elastic bandages were applied with the patient in the recumbent position and the foot in dorsal flexion. Elastic bandages

Table I. Characteristics of the treatment and control groups

Variable	*Treatment group (n = 75)*	*Control group (n = 7)*	P *value*
Male:female ratio	39:36	34:41	.41
Age (y)	55 (33-80)	57 (34-81)	.37
Previous episodes of ulceration (No)	5 (2-10)	5 (1-11)	.33
Size of the ulcer (cm^2)	72 (24-210)	64 (20-195)	.61
Duration of the ulcer (y)	7 (0.6-28)	6 (0.6-21)	.52

Data are median (range) unless otherwise noted.

were changed regularly every 3 months. The patient was advised to walk 30 minutes after bandaging.

Interface pressure was measured under the Trickovic sensor system (Nis, Serbia) with piezo resistance sensors at one site on the lower leg (8 cm above the medial malleolus) and with the patient in the supine position. The pressure was measured on three occasions, and the mean value for each patient was taken for statistical analysis.

End points and statistical analyses. The primary end point of the study was complete ulcer healing at 500 days. In cases in which the original ulcer closed but a new area developed on the same limb while the original ulcer was still present, the limb was considered to be open until this new area of ulceration had also closed. The definition of ulcer closure was the point at which complete epithelialization of the reference limb occurred. Patients with ulcer closure were provided in the control group with class II (20-25 mm Hg) compression hosiery (Rudo), whereas in the treatment group patients continued to wear the Tubulcus. Patients were followed up until 52 weeks to determine the recurrence rate.

Statistical methods. Log-rank life-table analysis was used to compare healing rates in the two treatment groups. Cox regression analysis with the backward method was performed to determine whether covariates (age, sex, ulceration surface, time since ulcer onset, previous operations, history of deep vein thrombosis, body mass index, and wound swabbing results) significantly influenced the time to healing. The Fisher exact test was used to compare categorical parameters between groups, and the Mann-Whitney *U* test was used to compare values of noncategorical parameters. Analyses were performed with SPSS 10.0 (SPSS Inc, Chicago, Ill).

RESULTS

Demographics and ulcer characteristics are listed in Table I. Both groups were well matched for age, sex, medical history, and ulcer characteristics. The mean patient age for the entire study population was 56 years (range, 33 to 81 years). Fifty-one percent of the patients were female, and 54% of the ulcers affected the left leg.

The median number of previous episodes of ulceration was 5 (range, 1 to 11). In the treatment group, 78% of ulcers were medial, 15% were lateral, 5% were circumferential, and 2% were a combination. In the control group, 81% of ulcers were medial, 11% were lateral, 4% were circumferential, and 4% were a combination. Twenty-five patients (35%) in the treatment group and 20 patients (30%) in the control group had previous deep vein thrombosis. No significant difference was observed between the treatment and control groups according to the CEAP classification (Table II).

Table II. Distribution of patients in the examined groups according to CEAP classification

Variable	*Treatment group*	*Control group*	P *value*
Clinical			
C6	72 (100%)	66 (100%)	
Etiologic			
Primary	42 (58%)	40 (61%)	
Secondary*	30 (42%)	26 (39%)	.78
Anatomic			
Deep	16 (22%)	19 (29%)	.49
Perforator	36 (50%)	31 (47%)	.72
Superficial + perforator	16 (22%)	13 (20%)	.72
Superficial + deep	4 (6%)	3 (5%)	.99
Pathophysiologic			
Reflux	61 (85%)	57 (86%)	
Reflux + obstruction	11 (15%)	9 (14%)	.78

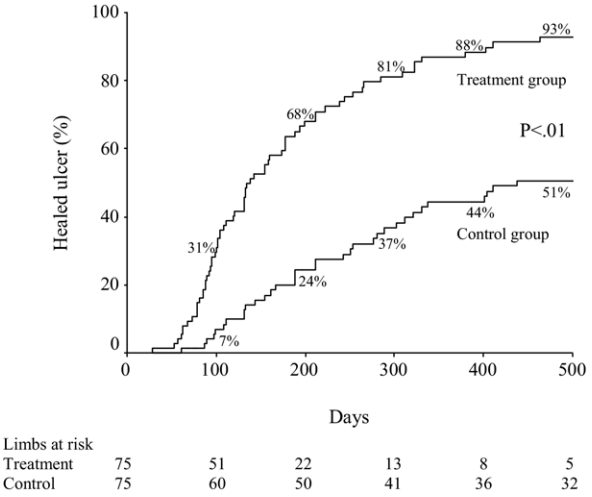
*Secondary etiology was based on ultrasound findings.

Pain, edema, pigmentation, and lipodermatosclerosis were present in all 138 patients (100%). In the treatment group, 14 patients (19%) had previously had stripping of great saphenous vein, and 5 patients (7%) had had a superficial endoscopic perforator vein surgery procedure. Twelve patients (18%) in the control group had previously had stripping of a great saphenous vein, and five patients (8%) had had a superficial endoscopic perforator vein surgery procedure. During the observation period, neither surgery nor sclerotherapy was performed in the patients included in the study.

Interface pressure in the treatment group was 50 mm Hg (range, 46 to 56 mm Hg) and was 44 mm Hg in the control group (range, 37 to 49 mm Hg). The bandaging systems were worn day and night. Although compliance was not formally assessed, there were no withdrawals from the study because of noncompliance. It is interesting that none of the patients included in this study had previously received compression therapy.

The median healing time in the treatment group was 133 days (range, 28 to 464 days), and in the control group it was 211 days (range, 61 to 438 days) (Graph 1). The ulcer with the largest surface in the treatment group and entire study, covering almost the entire circumference of the leg (210 cm^2), healed in 280 days (Figs 1 and 2).

The recurrence rate during the 1-year follow-up period was 24% (16/67) in the treatment group and was 53% (18/34) in the control group ($P < .05$). Among 34 recurrent ulcers in both groups, 14 (41%) occurred not at the original site of the ulcer, but below the medial malleolus. These recurrent ulcers were typically 2 × 1 cm in diameter,



Graph 1. Cumulative healing rate of venous leg ulcers in the treatment and control groups.

Fig 1. The ulcer with the largest surface in the entire study (210 cm^2) at the beginning of the treatment.

persistent, and difficult to treat. After additional compression treatment using the same treatment protocol, all 16 recurrent ulcers in the treatment group healed. In the control group, the healing rate for recurrent ulcers was 88% (16/18).

Lateral side ulcers seem to be more difficult to heal, but the sample size was too small to prove a statistically significant difference. There were no deaths or major complications in either group. Adverse events in the treatment group were skin excoriations on the front of the ankle and 1 inch below the knee (12/72; 17%). In 47% of patients (34/72), the upper end of the tubular device was hardly controlled, showing a tendency to slip below the knee and cause additional pressure and pain. In the control group, pain was present more often compared with the treatment group at the beginning of the treatment (19/66 [29%] vs 8/72 [11%]). The different variables analyzed for association with the outcome of compression therapy are listed in Table III. None was statistically significant.

Fig 2. Ulcer healed at the 280-day treatment mark.

Table III. Covariates entered into the Cox regression model with the backward method

Variables not in the equation	*OR*	*95% CI*	P *value*
Age	1.205	0.793-1.832	.38
Sex	0.997	0.975-1.019	.78
Ulceration surface	0.999	0.995-1.004	.82
Time since ulcer onset	1.001	0.998-1.003	.61
Previous operations	1.197	0.799-1.795	.38
History of deep vein thrombosis	0.883	0.554-1.409	.60
Body mass index	1.170	0.543-1.797	.56
Microbiologic status	1.044	0.915-1.173	.51
Emergence of new skin islets	1.731	0.996-2.466	.06
Reduction in calf circumference	1.524	0.995-2.053	.07

OR, Odds ratio; *CI,* confidence interval.

DISCUSSION

The goals of compression therapy in the treatment of venous leg ulcerations are healing ulcers, reducing pain and

edema, and preventing recurrence.[7] External compression of the calf muscle is achieved with compression hosiery or compression bandages. Two types of compression bandages are used for the treatment of venous leg ulcers: elastic and inelastic bandages. Inelastic bandages provide high pressure with muscle contraction (high working pressures) but limited pressure at rest. Conversely, elastic compression bandages provide sustained pressures and conform to the leg better.[8] Different bandaging systems have been developed for the treatment of venous leg ulcers (single-layer or multilayer bandaging systems). A well-known systematic review of compression treatment published in 1997 found that multilayer compression bandages were superior compared with single-layer bandage systems.[9] Multilayer bandaging systems were more effective compared with single-layer compression in four trials in the Cochrane Database Systemic Review published in 2001.[10] This review identified 22 trials reporting 24 comparisons. In five trials, elastic compression was more effective than nonelastic compression, whereas no difference in healing rates between four-layer and other high-compression multilayered systems was identified (three trials). Compression stockings were evaluated only in two trials. In first trial, a combination of a high-compression stocking and thromboembolism stocking was more effective than a short-stretch bandage. The second trial reported no difference between the compression stockings and Unna boots.

Published healing rates of venous ulcers obtained with compression therapy vary widely from 40% to 90%.[11-20] Further trials are necessary to identify the best treatment options, especially for nonhealing ulcers. A possible way to predict nonhealing venous leg ulcers is to examine the prognostic risk factors that are consistently found in a number of published studies (large wound area and wound of long duration). Wounds with either or both of these factors are at risk for not healing.[9] The results of our study do not support these findings. Large and long-lasting ulcers could be healed, although more time is needed. Most ulcers difficult to treat with compression therapy showing a nonhealing tendency in our study were the ulcers with the deepest presentation (>2 cm deep). Also, lateral ulcers were more difficult to treat, probably because it is difficult to achieve adequate compression. A decrease in wound size during the first 50 days of treatment is a favorable prognostic factor for healing. According to some studies, approximately 50% to 70% of venous ulcers with a decrease in wound size during the first month of compression therapy will be healed after 6 months of the treatment.[9] In our study, only five patients in the treatment group did not heal at the 500-day treatment mark. In three patients, the ulcer surface was considerably smaller (50%) compared with the beginning of the treatment, and in one patient the ulcer was smaller (30%). Only in one patient was no improvement seen. A wound swabbing in this patient showed the presence of β-hemolytic streptococcus group A, which may be the cause for nonhealing. In obese patients, more time is needed for ulcer closure. We think that the main reason for this is immobility and, therefore, inactivity of their muscle pump.

The good results achieved in our study in the treatment group could be to some extent due to the tubular form of the Tubulcus. A tubular form gives, in our opinion, the best support to the calf muscle and mimics muscle fascia. However, the Tubulcus by itself can not provide sufficient pressure to the calf muscle for the treatment of extensive ulcers. Sufficient pressure of 50 to 55 mm Hg was provided with an additional layer of elastic bandage. Further trials are needed to clarify the potential treatment benefits of this treatment combination (a tubular compression device plus an elastic bandage).

Disciplined high-pressure bandaging has the potential to heal large ulcers to a high degree. It is possible with high-pressure compression to decrease the recurrence rate during the first year after healing, but the long-term recurrence rate is not known.

CONCLUSION

This study suggests that for extensive venous ulceration, multilayer compression therapy with the Tubulcus provides a high healing rate. Sustained compression of 35 mm Hg is necessary after ulcer healing to avoid recurrence.

AUTHOR CONTRIBUTIONS

Conception and design: DJM, SSZ, DCB, ZDP
Analysis and interpretation: DJM, SSZ, DCB
Data collection: DJM, SSZ, ZDM, BMJ
Writing the article: DJM, ZDP, BMJ
Critical revision of the article: DJM, SSZ, ZDP
Final approval of the article: DJM, SSZ, ZDP, ZDM, BMJ
Statistical analysis: DCB, ZDM
Obtained funding: ZDP, BMJ
Overall responsibility: DJM

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